TB Drugs in the Pipeline: What to Expect & When

Stephen Murray, MD, PhD
FIND, TB Alliance Symposium
October, 2013
TB Alliance

• Founded in 2000
• Not-for-profit Product Development Partnership (PDP) headquartered in New York
• Entrepreneurial, virtual approach to drug discovery and development
• Largest portfolio of TB drug candidates in history
TB Alliance Mission

- Develop new, better treatments for TB
- Ensure that new regimens are Affordable, Adopted for use, and made widely Available (AAA strategy)
- Catalyze global TB drug development activities
# Current Therapy and Unmet Needs in TB

<table>
<thead>
<tr>
<th>Drug Sensitive TB</th>
<th>M(XDR)-TB</th>
<th>TB/HIV con-infection</th>
<th>Latent TB Infection</th>
<th>Children</th>
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<tbody>
<tr>
<td>Current Therapy</td>
<td>Injections and drugs taken for more than 2 years, poorly tolerated</td>
<td>Drug-drug interactions with ARVs</td>
<td>9 months of isoniazid</td>
<td>No adequate dosing formulations</td>
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<td>Unmet Needs</td>
<td>Shorter, simpler therapy</td>
<td>More effective, shorter, safer simpler regimens</td>
<td>Co-administration with ARVs</td>
<td>Adequate dosing regimens and formulations</td>
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</table>

**Current Therapy**
- Drug Sensitive TB: 4 drugs taken for 6 or more months
- M(XDR)-TB: Injections and drugs taken for more than 2 years, poorly tolerated
- TB/HIV con-infection: Drug-drug interactions with ARVs
- Latent TB Infection: 9 months of isoniazid
- Children: No adequate dosing formulations

**Unmet Needs**
- Drug Sensitive TB: Shorter, simpler therapy
- M(XDR)-TB: More effective, shorter, safer simpler regimens
- TB/HIV con-infection: Co-administration with ARVs
- Latent TB Infection: Shorter, more easily tolerated therapy
- Children: Adequate dosing regimens and formulations

**TB ALLIANCE**
### Global TB Drug Pipeline

#### Preclinical Development

- **Early Stage Development**
  - CPZEN-45
  - DC-159a
  - Q203
  - SQ609
  - SQ641
  - TBI-166

- **GLP Tox.**
  - PBTZ169
  - TBA-354

#### Clinical Development

- **Phase I**
  - AZD5847<sup>N</sup>
  - Bedaquiline<sup>N</sup><sup>c</sup><sup>R</sup>
  - Linezolid
  - PA-824<sup>N</sup><sup>c</sup>
  - Rifapentine
  - SQ-109<sup>N</sup>
  - Sutezolid<sup>N</sup>

- **Phase II**
  - Delamanid<sup>N</sup><sup>R</sup>
  - Gatifloxacin<sup>c</sup>
  - Moxifloxacin<sup>c</sup>
  - Rifapentine<sup>R</sup>

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Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone


2. Drug candidate currently in combination regimen in clinical testing

3. Submitted for approval or approved by stringent regulatory authority (i.e., FDA, EMA, WHO Prequalification)

4. New chemical entity

**Updated: June 2013**
<table>
<thead>
<tr>
<th>LEAD IDENTIFICATION</th>
<th>LEAD OPTIMIZATION</th>
<th>PRECLINICAL DEVELOPMENT</th>
<th>PHASE 1</th>
<th>PHASE 2A</th>
<th>PHASE 2B</th>
<th>PHASE 3</th>
<th>PHASE 4</th>
</tr>
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<tbody>
<tr>
<td>ATP Synthesis Inhibitors</td>
<td>Mycobacterial Gyrase Inhibitors</td>
<td>TBA-354</td>
<td>NC-003</td>
<td>NC-002</td>
<td>REMox-TB</td>
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<td>Energy Metabolism Inhibitors</td>
<td>Pyrazinamide Analogs</td>
<td>TBI-166 IMM</td>
<td>PA-824/</td>
<td>PA-824/</td>
<td>Moxifloxacin/</td>
<td>Bayer, MRC, UCL</td>
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<td>AZ/University of Penn</td>
<td>Yansei University</td>
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<td>Bedaquiline/</td>
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<td>Rifampin/</td>
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<td>Whole-Cell Hit-to-Lead Program</td>
<td>Diaryquinolines Janssen/University of Auckland/UIC</td>
<td>Preclinical TB Regimen</td>
<td>Pyrazinamide</td>
<td>Clofazimine/</td>
<td>Pyrazinamide/</td>
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**TB Alliance R&D Partners:**

- AstraZeneca (AZ)
- Bayer Healthcare AG (Bayer)
- Beijing Tuberculosis and Thoracic Tumor Research Institute
- Calibr
- GlaxoSmithKline (GSK)
- Institute of Materia Medica (IMM)
- Janssen (Johnson & Johnson)
- Johns Hopkins University (JHU)
- Medical Research Council (MRC)
- Novartis Institute for Tropical Diseases (NITD)
- New York Medical College
- Rutgers University
- Sanofi
- Stellenbosch University
- University College London (UCL)
- University of Auckland
- University of Illinois at Chicago (UIC)
- University of Pennsylvania School of Medicine
- Yonsei University
REMox TB: A Global Phase 3 Trial

Results expected in 2014

• Evaluating if a 4-month moxifloxacin-based regimen can perform as well as the current 6-month standard of care in drug-sensitive TB patients.
  – Potential to be first new drug to treat drug-sensitive TB in nearly 50 years
  – Potential to shorten treatment by 33%
  – Potential to significantly reduce economic impact of TB on patients due to shorter regimen

Enrollment completed in January 2012; registration expected in 2014
Unified Drug Sensitive/Drug Resistant Regimen Development Path

<table>
<thead>
<tr>
<th>Stage</th>
<th>Pre clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<tbody>
<tr>
<td>Testing Model</td>
<td>Mouse Model</td>
<td>Healthy Subjects</td>
<td>Monotherapy 2-Week EBA</td>
<td>Combination/Regimen EBA</td>
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</tbody>
</table>
| Study Attributes | • Single drug  
• Combo in regimen  
• Relapse-free sterilizing activity  
• Single and repeat dose  
• Safety, tolerability  
• PK  
• Drug Interactions | • Single drug  
• Dose ranging  
• DS patients only | • Optimized dose Regimen  
• Test final regimen  
• DS patients only? | • DS and DR sensitive to regimen  
• DS vs HRZE standard  
• DR for consistency |

Go/No-Go Criteria:
- PK to support daily dosing
- Clear effect to reduce CFU count
- As good as HRZE standard
- Better Than HRZE

2 to 4 month treatment, eg  
DS vs HRZE for non-inferiority  
DR for consistency
PaMZ is being investigated in both TB and MDR-TB patients in the 8-week study NC-002. It successfully completed a two-week clinical study (NC-001) in 2011.

Results:
- PaMZ compares favorably to the standard of care
- shows potential to treat both drug-sensitive and drug-resistant TB in four months with a single combination treatment
- validates the paradigm of novel regimen development
- supports predictive capability of mouse model
First Novel Combo SSCC: NC-002
In patients with TB sensitive to Pa, M, and Z
Participants with newly diagnosed smear positive DS and MDR TB

Randomize

DS

Pa(200mg)-M-Z
N=60

Pa(100mg)-M-Z
N=60

Rifafour
N=60

DR

Pa(200mg)-M-Z
N=24

2 months of treatment

Serial 16 hour pooled sputum samples for CFU Count

Z = pyrazinamide    Pa = PA-824    M = moxifloxacin
Novel Regimens in Development

NC-003 trial

Next generation regimens in the clinic

NC-003: Multiple-arm trial testing new regimens

- NC-003 is a multiple-arm study testing additional new TB regimens with the potential to even further shorten treatment for TB and MDR-TB
  - 2-week “EBA” trial
  - Trial includes multiple combinations consisting of bedaquiline, PA-824, pyrazinamide, and clofazamine
  - Regimens included in trial were identified as especially promising via TB Alliance Preclinical Regimen Identification Program
Third Novel Combo EBA: NC-003

Z=pyrazinamide, C=clofazimine, Pa=P-824, J=bedaquiline

- Participants with newly diagnosed smear positive DS TB

Randomize 15 per group

Serial 16 hour pooled sputum samples for CFU count

14 daily doses
Launch Dates and DST Requirements

• Bedaquiline - Launched
  – Indication: single-drug addition to existing therapy in MDR

• Delamanid - Potentially very soon
  – Indication: single-drug addition to existing therapy in MDR

• REMoxTB - 2015
  – Indication: DS-TB (HRZM or MRZE)
  – Should not be used in MDR-TB
    • DST for MDR required before start of treatment (unless epidemiology/surveillance indicates no significant MDR-TB in area)

• PaMZ (NC-002 regimen) - Potential Phase 3 2014
  – Indication: TB sensitive to Pa, M, and Z
    • M sensitivity testing required in areas with significant M resistance
    • Z sensitivity testing required, but R sensitivity indicating DS-TB may be a sufficient proxy
TB Alliance Supporters

Thanks to all those who support our mission for better, fast TB drugs
Thank you!